

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of
KAWADA, Kenji et al.
Serial No.: 09/214,277
Filed: March 1, 1999
NOVEL PARA-TERPHENYL COMPOUNDS

DECLARATION UNDER 37C.F.R. 1.132

Honorable Commissioner
of Patents and Trademarks
Washington, D. C. 20231

Sir:

I, Dr. Masashi Deguchi, declare and states as follows:

I am a Japanese citizen of Hyogo, Japan.

I graduated from Kyoto University, Department of Science in March, 1994 and my degree is entitled Ph. D of Science.

Since April, 1994, I have been employed by Shionogi & Co., Ltd. and have been engaged in research work in the Drug Discovery Laboratories, SHIONOGI at 1-1, Futabacho 3-chome Tbyonaka-shi, Osaka, Japan.

I am one of the researchers of the subject matter of United States Patent Application Serial No. 09/214,277 filed on March 1, 1999 and I am intimately familiar with the contents of the application.

The terphenyl compounds of the present invention are structurally similar to constituent molecules of liquid crystal. We examined the suppressive effect of these liquid crystal-related compounds on the IgE production against ovalbumin (OVA) with the method described below.

EXPERIMENT

BALB/c mice were immunized by an intraperitoneal administration of 0.2 ml suspension of 2 µg of ovalbumin (OVA) and 2 mg of aluminium hydroxide gel in physiological saline. After the liquid crystal-related compounds and compound of the

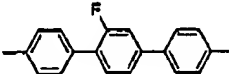
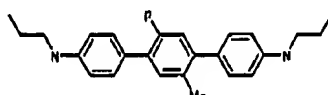
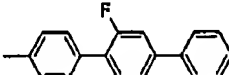
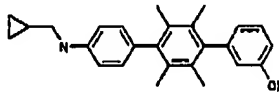
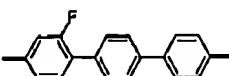
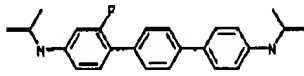
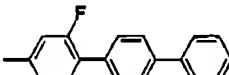
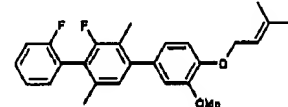
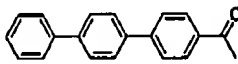
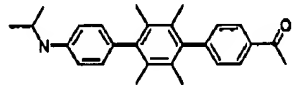
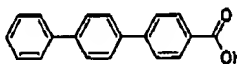
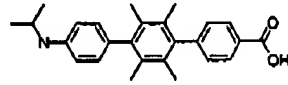
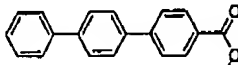
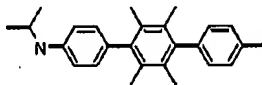
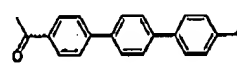
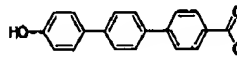
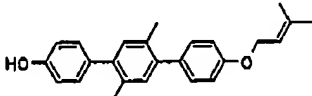
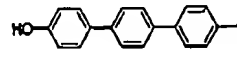
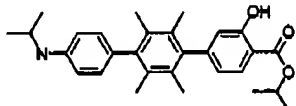
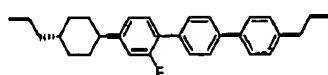
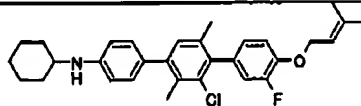
present invention was dissolved or suspended in N, N-dimethylacetoamide, the mixture was diluted 20 times with miglyol 812 neutral oil. The obtained solution was orally administered to mice at 0.1 ml per mouse (dose 40 mg/kg). The administration was continued for 10 days from the immunizing day to the day before the blood collection. 10 days after the immunizing day, blood was collected from hearts, then sera were separated and stocked at -40 °C till the measurement of IgE antibody titer. The obtained mouse serum was 2-fold diluted with physiological saline, then each 50 µl of the solution was intradermally injected at dorsal skin of Wistar rats which previously hair cut. After 24 hours, a passive cutaneous anaphylaxis reaction (PCA) was induced by an intravenous injection of 0.5 ml of physiological saline containing 1 mg of OVA and 5 mg of Evans' blue dye. The rats were sacrificed 30 minutes later and the highest dilution giving bluing with a diameter of 5 mm or more was recorded as the PCA titer. For example, when a serum is positive for the PCA reaction till 2^7 times dilution, the anti-OVA IgE antibody titer of the mouse is defined.

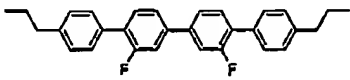
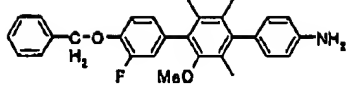
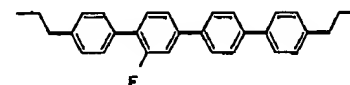
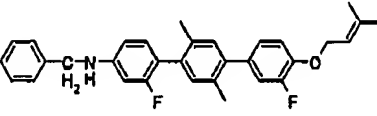
RESULT

1) IgE production suppressive activity of liquid crystal-related compounds and the compounds of the present invention

As shown in Table 1, we found that none of the assessed liquid crystal-related compounds had suppressive effects on the IgE production. On the other hand, the compounds of the present invention similar to the liquid crystal-related compounds have the suppressive effects.

Table 1

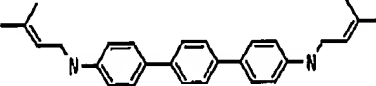
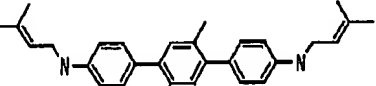
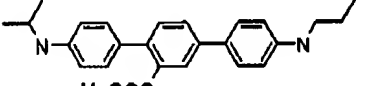
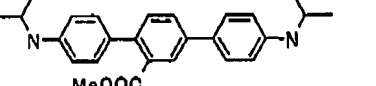
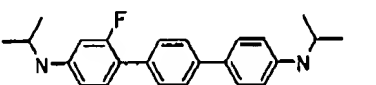
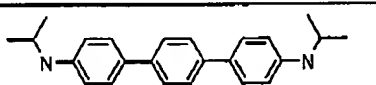
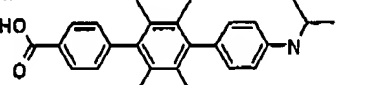
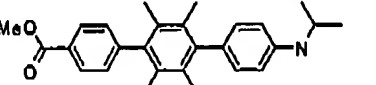
Reference compounds			PCA	compounds of the present invention	PCA
U.S. 4,594,465	column 11 & 12		10.7		0.3
	column 11 & 12		10.7		2
	column 21 & 22		10.3		<0
	column 21 & 22		10		<0
U.S. 5,417,885	column 9 compound 1-3		9.7		<0
	column 10 compound 2-3		10		5
	column 10 compound 3-3		10		1
	column 10 compound 4-3		10.3		
	column 10 compound 6-3		10.7		5.2
	column 10 compound 7-3		10.7		2
GB2,240, 778	page 12 compound (2)		9.7		4.3

page 12 compound (12)		10.7		6.7
page 12 compound (17)		10.5		0

2) Affection on the IgE production suppressive activity of the substituents

We examined the affection on the IgE production activity of the substitution in a terphenyl system.

Table 2

	PCA		PCA
	7		<0
	7		<0
	3.5		
	5		
	5		1

As shown in Table 2, a small modification of a terphenyl compound has unexpected high effects on the IgE production suppressive activity.

CONCLUSION

Even though the liquid crystal-related compounds and the compounds of the

present invention have similar structures, it is unexpected that the compounds of the present invention have IgE production suppressive activity.

I hereby declare that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date September 17, 2002

By Masashi Deguchi